35. (Four Times Amended) A method for the *in vitro* construction of SV40 pseudoviruses comprising a non-viral constituent wherein said non-viral constituent comprises purified exogenous antisense RNA, or purified exogenous ribozyme RNA or purified exogenous RNA or purified exogenous non-viral DNA which inhibits or prevents the expression of undesired protein or proteins in a mammalian cell, comprising the following steps:

a) allowing a semi-purified or pure SV40 VP1 capsid protein or a mixture of VP1 and at least one other SV40 protein to self assemble into SV40-like particles and

b) bringing said SV40-like particles obtained, in step (a) into contact with said purified exogenous antisense RNA, or purified exogenous ribozyme RNA, or purified exogenous RNA or purified exogenous non-viral DNA which inhibits or prevents the expression of undesired proteins in a mammalian cell, to give *in vitro* constructed SV40 pseudoviruses.

37. (Thrice Amended) A method according to Claim 35 wherein in step (a) at least one other SV40 protein, preferably SV40 agnoprotein, is added to the mixture of SV40 capsid protein or proteins and the purified exogenous antisense RNA or purified exogenous ribozyme RNA or purified exogenous RNA or purified exogenous DNA.

43. (Thrice Amended) An *in vitro* method of transforming a purified exogenous DNA, purified exogenous RNA, purified exogenous antisense RNA, purified exogenous ribozyme RNA, purified exogenous protein or peptide product into a cell comprising infecting said cell with the construct of Claim 1.

47. (Amended) A complex comprising semi-purified or pure SV40 VP1 capsid protein or a mixture of VP1 and at least one other SV40 capsid protein, and a non-viral constituent, wherein the non-viral constituent is a purified exogenous protein or peptide.

REMARKS

Claims 1-2, 4-13, 16-20, 22-37, 41-43 and 45-47 are currently pending in the application. Claims 1, 6-13, 18, 20, 25, 28-29, 35, 37, 43 and 47 are amended. The amendments find support

regulatory element." And on page 17, lines 12-14, the specification states that "SV40 derived *ori* DNA sequence may be added and said exogenous nucleic acid optionally has DNA sequence encoding one or more regulatory elements".

Applicants believe that one of ordinary skill in the art, having read these passages, would then approach the text on page 19 (lines 17-20) in a different light than that viewed by the Examiner. This section states that the constructs of the invention are very efficient in gene transfer and may be suitable for treating a wide spectrum of diseases, and that "[p]lasmids carrying the desired gene and the SV40 *ori* and, optionally *ses*, are encapsidated in COS cells, optionally with helpers, as SV40 pseudovirions, and transmitted into the target cells by viral infection." That is, Applicants believe that one of ordinary skill in the art would view this as one embodiment among other embodiments of the claimed invention. That is, one of skill could (emphasis added) make plasmids carrying the desired gene and the *ori* and *ses* sequences, encapsidate them into COS cells as pseudovirions and transmit them by viral infection.

Likewise, the text on page 20 (lines 19-24) also confirms that the *ori* sequence is optional. This section states that "An additional important advantage is that the *ses* element is not required for in vitro packaging . . . reducing the size of the SV40 sequences to about 100 bp, comprising the *ori*, **in the exemplified experiments**. Embodiments without even this element are also contemplated. In the present examples, the *ori* element was required for the assay of infectious units."

This text passage therefore describes an advantage of the invention, that the constructs contain little required DNA. It also states that in the examples, *ori* is always included so that the infectious units could be assayed, thereby showing that the invention works and provides a surprisingly high level of infectivity. The invention includes embodiments that do not include *ori* since it is not necessary except for assaying infectious units. The ori sequence is something that the inventors included only to demonstrate the superiority of the invention over the methods in the art at that time.

Applicants therefore respectfully submit that the specification clearly states that the *ori* sequence is optional, and that the specification carefully explains why, if *ori* is optional, it was included in the constructs of the examples. Moreover, the Declaration of Ms. Shaul, which was previously submitted, provides evidence that the ori sequence is not required for packaging. Applicants respectfully request that the rejection on this basis be reconsidered and withdrawn.

in the application as filed, and are discussed in the relevant sections below. No new matter is added by these amendments.

Telephonic Interviews

Applicants thank the Examiner for the telephonic interview of December 20, 2001, between the Examiner and the Applicants' representatives, Doreen M. Hogle and Joyce C. Hersh, and for the review of a draft Amendment and telephonic interview of February 25, 2002 with Doreen M. Hogle.

In the Office Action, the Examiner stated that the Declaration under 37 C.F.R. 1.132 is insufficient to overcome the rejections because the Declaration was unsigned.

During the telephonic interview of December 20, 2001, Applicants' representatives pointed out that the Declaration was in fact signed by the Declarant, Orly Ben-Nun-Shaul. Upon reviewing the file, the Examiner agreed that the Declaration had been signed, and stated that it would be entered and considered as evidence. As a convenience to the Examiner, a copy of the Declaration is again submitted herewith.

Claim Rejections Under 35 U.S.C. § 112, First Paragraph

Claims 1-2, 4-8, 10-18, 16-20, 22-26, 28-37, 41-43, and 45-46 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is nearly connected, to make and/or use the claimed invention. Specifically, the Examiner stated in the Office Action that since claims 19 and 27 specifically recite the *ori* sequence, the remaining claims therefore do not need the *ori* sequence, but that the specification (at pages 19-20) makes clear the necessity of having an *ori* sequence in each nucleic acid which is encapsidated in the claimed SV40 protein capsid structures.

As discussed in the telephonic interview in December, Applicants respectfully disagree with this interpretation of the text. Other portions of the specification make clear that the *ori* sequence is optional, and not necessary to practice the invention. For instance, on page 5, lines 13-14, the specification clearly states that "[t]he constructs of the invention may comprise SV40 derived *ori* DNA sequence" (emphasis added). Page 13, lines 6-7, state that "[t]he constructs of the invention may optionally comprise SV40-derived *ori* DNA sequence as said replication

Claim 43 is also rejected under 35 U.S.C. § 112, first paragraph, the Examiner stating that the specification, while being enabling for *in vitro* use of the method of transforming a cell with a construct of SV40 viruses or pseudoviruses comprising exogenous nucleic acid and at least one pure or semi-purified SV40 capsid protein, does not reasonably provide enablement for *in vivo* use of the method of transforming a cell with a construct of SV40 viruses or pseudoviruses comprising exogenous nucleic acid and at least one pure or semi-purified SV40 capsid protein, which constitutes gene therapy.

Applicants respectfully disagree. However, solely to speed prosecution, Applicants have amended the claim as suggested by the Examiner to recite an *in vitro* method of transforming a cell. Applicants therefore respectfully request that the rejection on this basis be reconsidered and withdrawn.

Claim Rejection Under 35 U.S.C. § 112, Second Paragraph

Claim 47 is also rejected under 35 U.S.C. §112, second paragraph as being indefinite for failing to point out and distinctly claim the subject matter which Applicant regards as the invention. Specifically, the Examiner believes that there is no definition for "peptide product", and that the claim is therefore vague and indefinite.

Applicants have amended Claim 47 to delete the term "product", thus, clarifying the claimed subject matter Applicants have also amended Claims 1, 6-8, 10-12, 25 and 28 to also delete the term "product". The rejection is therefore moot, and withdrawal is requested.

Claim Rejection Under 35 U.S.C. §102(b)

Claims 1-2, 4-7, 9-10, 12, 16-20, 22-25, 27-34, 41-42 and 47 are rejected under 35 U.S.C. § 102(b) as being anticipated by Christensen *et al.* (of record). Specifically, the Examiner responds to Applicants' arguments set forth in the previous Reply by saying that Christensen *et al.* teaches that assembly of pseudoviruses was attempted using a exogenous source of viral DNA, *i.e.*, SV40 nucleoprotein complex and empty virion shells, and that Christensen *et al.* therefore fulfills the limitations as set forth in the claims.

This issue was discussed with the Examiner in the December telephonic interview. The Examiner stated that the DNA used in Christensen *et al.* was nucleoprotein, not naked DNA, and that addition of a limitation reciting naked DNA could avoid the anticipatory rejection.

During the December telephonic interview, it was agreed that the phrase "purified DNA" would be more appropriate. Applicants have therefore amended Claims 1, 6, 9, 10, 13, 18, 20, 25, 28-29, 35, 37, 43 and 47 to recite purified exogenous DNA. Claims 2, 4-5, 7, 10, 12, 16-17, 19, 22-24, 27, 30-34 and 41-42 depend from the amended claims and thus carry the same limitations. As amended, the claimed invention is distinguished from Christensen *et al.* Applicants respectfully request that the rejection on this basis be reconsidered and withdrawn.

Claims 1-2, 4-7, 9-10, 12, 16-20, 22-25, 27-34 and 41-42 are also rejected under 35 U.S.C. § 102(b) as being anticipated by Colomar *et al.* (of record). Applicants have amended Claims 1, 6, 12, 13, 18, 28, 29, 35 and 47 to recite that the complex comprises semi-purified or pure SV40 capsid proteins and a non-viral constituent. Claims 2, 7, 9-10, 12, 16-17, 19-20, 22-25, 26-27, 30-34 and 41-42 depend from the amended claims and thus carry the same limitations.

During the telephonic interview of February 25, 2002, the Examiner requested that specific support be pointed out for the term "non-viral" as it may constitute new matter. Support for these amendments is found throughout the Specification. The plain meaning of the term "non–viral" is "not of virus origin". The specification describes in numerous places that the exogenous constituent is a constituent of non-viral origin. See, for example, in the specification on page 4, lines 11-24; page 5, lines 17-26; and page 11, lines 13-24. More specific examples can be found on page 13, lines 2-5 which describe the exogenous non-viral constituent beta-globin; page 14, lines 16-26 which describe the use of anti-sense oligonucleotides to inhibit *bcr/abl* transcripts; and page 15, lines 17-26 which describe packaging fibroblast growth factor. Table 3 on page 33 of the specification lists beta-globin, beta-globin plus the LCR element and MDR1 as exogenous non-viral constituents packaged in the constructs of the invention.

It is axiomatic that any claim amendments must be supported by the specification to avoid written description or new matter rejections. However, as stated in the MPEP § 2163.07, the subject matter of the claim "need not be described literally (i.e., using the same terms or *in haec verba*) in order for the disclosure to satisfy the description requirement." It is clear that exogenous, non-viral constituents are described in the specification and that, although the term "non-viral" does not literally appear, it is clearly encompassed by the descriptions in the specification detailed above.

Merely rephrasing passages of the specification does not constitute new matter when the same meaning remains intact. The mere inclusion of an art-recognized term, such as non-viral,

would not be considered new matter in this case. One of skill in the art, reviewing the above-identified passages from the specification, would clearly recognize that the exogenous constituent can be of non-viral origins.

Neither Colomar *et al.* nor Christensen *et al.* describe pseudoviruses comprising semipurified or pure SV40 capsid proteins and a non-viral constituent. Both Colomar *et al.* and Christensen *et al.* used only viral constituents, and thus the claimed complexes are novel over the described constructs

Moreover, the packaging of non-viral DNA is not taught by either Colomar or Christensen. Colomar states (page 2785, col. 1) that "We wanted to test whether the proteins forming the disassembled subunits of SV40 could be induced to disassociate from and re-associate with the viral DNA". Christensen *et al.* used nucleoprotein complexes which contained SV40 DNA, and thus the term non-viral also distinguishes over Christensen *et al.* In contrast, the claimed complex of the present invention comprises viral capsid proteins and non-viral constituents. Thus, the pseudovirions of Colomar *et al.* and Christensen *et al.* do not anticipate the claimed invention and reconsideration and withdrawal of the rejections is requested.

Claim Rejections Under 35 U.S.C. § 103(a)

Claims 1-2, 4-13, 16-20, 22-37 and 41-47 are rejected under 35 U.S.C. § 103 (a) as being unpatentable over Christensen *et al* or Colomar *et al.*, each in view of Carswell *et al.*, Oppenheim *et al.* and U.S. Pat. No. 5,863,541. Specifically, the Examiner believes that either Christiansen *et al.* or Colomar *et al.* teach the present invention, and the combination of these references renders obvious Applicants' invention.

The teachings of cited references have been discussed in detail in the Amendments filed in response to previous Office Actions, and are part of the record. As stated above, neither Christensen *et al.* nor Colomar *et al.* teach Applicants' invention, and combining either or both of these references with Carswell *et al.* and Oppenheim *et al.* fails to render obvious Applicants' invention.

In the present Office Action, the Examiner has stated that it would have been obvious to modify the method of Christensen *et al.* or Colomar *et al.* with the methods of the other three references to produce the instant invention, "because the capsid proteins of US Pat No. 5,863,541 *were assembled in a like manner to the instant claimed invention*, and inclusion of nucleic acids

which encode various therapeutic entities *is an obvious extension* of the gene therapy teachings of Christensen et al. or Colomar et al." (emphasis added). Applicants believe that the Examiner is using the Applicants' invention as a blueprint to assemble the cited references. This is impermissible hindsight. "Combining prior art references without evidence of such a suggestion, teaching, or motivation simply takes the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability -- the essence of hindsight." *In re Dembiczak* (50 USPQ2d 1614 (Fed. Cir. 1999)).

As discussed above, neither Christensen *et al.* or Colomar *et al.* teach or suggest pseudoviruses comprising SV40 capsid proteins and non-viral constituents. Christensen and Colomar merely teach the disruption and reassembly of viruses and do not teach or suggest that taking SV40 VP1 capsid proteins in combination with other non-viral constituents to form infectious particles.

At the time of the invention, a person of skill in the art knew that for the DNA to be packaged, it had to be highly compacted in order to fit into the limited space available within the SV40 capsid. In nature, high compaction is achieved by the histone proteins that are complexed with viral DNA of SV40 or related viruses (such as polyomavirus). Therefore, both Christensen *et al.* and Colomar *et al.* attempted to package nucleoprotein complexes (Christensen p. 438, second column from the middle; Colomar p. 2784 end of first paragraph).

The organization of nucleosomes around the SV40 minichromosome was shown to be critical for virus assembly. The positioning of nucleosomes and the ability of the nucleoprotein complex to compact, are determined in part by the primary sequence of the DNA. Because of these constraints, many DNA molecules (of the correct size) are not capable of appropriate compaction by histone proteins in order to be packaged. Colomar *et al.* used polyoma DNA as it is very similar to SV40 (page 2784, col. 1, line 4) and must be capable of similar compaction, since the space within the polyoma capsid is similar to the space in SV40. This is why, at the time of the invention, packaging of non-viral DNA was not attempted.

Th procedure of refolding taught by Colomar *et al.* included a step of reconstitution of nucleoprotein complex from polyoma DNA and histone proteins present in the reaction (page 2779 col. 2, last sentence; p. 2784, col. 1, first paragraph last sentence). Only afterwards did they lower the pH to 7.2 and added $CACl_2$ to allow reconstitution of the particles. Their method is not relevant to packaging of purified DNA in the absence of histone proteins, as in the present

invention.

Moreover, as described in Colomar *et al.* "The infectivity in mouse cells of the polyomavirus DNA reconstituted with SV40 proteins was tested by a DNA replication assay similar to that shown in Fig. 5a. It was found to be low, about the same as that of naked polyomavirus DNA". In contrast, the claimed constructs are significantly more infective than the naked (background, control) DNA as shown in Fig. 2.

U.S. Pat. No. 5,863,541 teaches the production of AAV capsids which may be used to transfer native or heterologous molecules into appropriate host cells. This reference does not teach construction of SV40 pseudoviruses comprising exogenous nucleic acid or exogenous proteins or peptides, nor does it make any suggestion to do so. It teaches methods of producing capsids for a completely different type of virus. SV40 is a member of the papova family and belongs to Class I, which is composed of the double-stranded circular DNA viruses. AAV is a member of the replication-defective *Dependovirus* genus of the parvovirus family, which belongs to Class II, which is composed of single-stranded linear DNA viruses. SV40 is an autonomous virus, capable of infecting the host and propagating on its own. In contrast, the members of the *Dependovirus* genus of the parvovirus family are entirely dependent on adenovirus or herpesvirus superinfection for the provision of further helper functions essential for their replication. The mechanism of DNA replication of the AAV single-stranded genome is also very different from that of SV40, in which ITRs (which are unique to AAV) play a major role. This mechanism is very different from the mechanism of replication of the double-stranded circular SV40 DNA, which is a minichromosome. Importantly, AAV assembles by the introduction of genetic material into pre-formed capsids, a mechanism completely different from that of SV40.

In addition, U.S. Pat. No. 5,863,641 teaches the production of recombinant AAV capsid proteins, expressed from an adenoviral vector, and their use for *in vivo* encapsidation of AAV vector DNA into infectious viral capsids, and not the *in vitro* construction of SV40 pseudoviruses.

U.S. Pat. No. 5,863,541 suggests isolating AAV capsids produced *in vivo*, disassembling them by known techniques, and allowing them to re-assemble in the presence of the desired constituents. However, this method was tried for SV40 capsids in Christensen *et al.*, and again by Colomar (*J. Virol.* 67:2779-2788, 1993), and failed in both cases. The findings of Christensen *et al.* are described above. Colomar *et al.* attempted to package foreign viral DNA (polyoma

virus DNA) in the disassembled SV40 particles. The titer of the reassembled particles decreased by 10,000-fold compared to the titer of the original virion preparation. Furthermore, Colomar *et al.* found that the particles containing foreign DNA had no biological activity, and were not infective. Therefore one of ordinary skill, applying the protocols described in U.S. Pat. No. 5,863,641 to SV40 would have failed to make Applicants' invention.

The Examiner also states that Carswell *et al.* (*J. Virol.* 60:1055-1061, 1986) teaches "the advantage of combining an SV40 agnoprotein with SV40 capsid proteins to facilitate the assembly of capsids." This reference shows that mutants which make no agnoprotein display abnormal perinuclear-nuclear localization of VP1, the major capsid protein (see Abstract), and that at least one function of the agnoprotein is to mediate the efficient localization of VP1 to the nuclear region, presumably so that the protein can participate in encapsidation (bottom of first column). However, this reference does not teach the making of constructs as described in the present invention, nor does it make any suggestion to do so. Rather, the goal of Carswell *et al.* is to elucidate the function of the SV40 agnoprotein, which was found to be the enhancement of the efficiency of localization of VP1 to the nuclear region. Nothing in Carswell *et al.* teaches or suggests assembly of constructs containing exogenous nucleic acids similar to those described in the instant application. Thus, the combination of the teachings of Carswell with the teachings of the '641 patent, Christensen and Colomar do not arrive at Applicant's claimed invention.

The Office Action states that Oppenheim *et al.* (*Proc. Natl. Acad. Sci. USA* 83:6925-6929, 1986) teaches the advantage of combining an SV40 *ori* with SV40 capsid proteins to facilitate the assembly of capsids. Oppenheim *et al.* teach SV40 pseudovirions that contain the CAT reporter gene. Oppenheim *et al.* do not teach how to make or use the constructs, virions or pseudovirions of the present invention. The constructs of Oppenheim *et al.* do not contain an exogenous nucleic acid encoding a therapeutic gene product. Oppenheim *et al.* teach plasmids containing *ori*, or *ori* and *ses* that have little or no CAT activity (a measure of gene expression). In addition, Applicants have found that *ses* is required for *in vivo* packaging, but not *in vitro* packaging (specification, page 30). Therefore, combining the teaching of Oppenheim *et al.* with the other cited references do not render obvious constructs for expression of a protein product, as claimed in the instant application.

The Examiner has not pointed to any specific passages in the cited references which provide motivation to combine those references, nor to any other sources for such motivation.

Rather, the Examiner relies on statements that "it would have been obvious . . . to modify the method" of the references to produce Applicants' invention, that portions of Applicants' invention "is an extension" of the methods of a reference, that "it is assumed" that the making of AAV pseudovirions and SV40 virions "is equivalent" for the purpose of delivering exogenous nucleic acids and proteins to cells, that the references "merely taught well known and advantageous methods" of facilitating the assembly of SV40 capsid proteins into SV40 capsids, or that the references are "justifiably combined" because they are "used to demonstrate well known and obvious elements which are used to study related subject matter". The Examiner has not stated with any specificity why one of ordinary skill in the art at the time the invention was made would be motivated to combine the cited references and passages therein to produce Applicants' invention.

The Examiner must state *why* one of ordinary skill would be motivated to combine the references, *e.g.*, from the references themselves, from the knowledge of one of ordinary skill, or the nature of the problem to be solved. "[T]he references must expressly or impliedly suggest the claimed invention or the examiner must present a convincing line of reasoning as to why the artisan would have found the claimed invention to have been obvious" (*Ex parte Clapp*, 227 USPQ 972, 973 (Bd. Pat. App. & Inter. 1985)).

The fact that references can be combined or modified is not sufficient to establish *prima facie* obviousness ("The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. MPEP § 2142, citing *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990)). In addition, the fact that the claimed invention is within the capabilities of one of ordinary skill in the art is not sufficient by itself to establish *prima facie* obviousness:

> A statement that modifications of the prior art to meet the claimed invention would have been " 'well within the ordinary skill of the art at the time the claimed invention was made' " because the references relied upon teach that all aspects of the claimed invention were individually known in the art is not sufficient to establish a prima facie case of obviousness without some objective reason to combine the teachings of the references.

MPEP § 2142, citing *Ex parte Levengood*, 28 USPQ2d 1300 (Bd. Pat. App. & Inter. 1993).

The Examiner has failed to provide motivation for the combining of the references, and has also failed to establish that the cited references disclose Applicants' invention. A *prima facie* case of obviousness has therefore not been made. Applicants respectfully request that the

rejection under 35 U.S.C. § 103(b) be reconsidered and withdrawn.

Claims 14 and 38 have been rejected under 35 U.S.C. § 103 (a) as being unpatentable over Christensen *et al.* or Colomar *et al.* each with Carswell *et al.*, Oppenheimer *et al.*. and U.S. Pat. No. 5,863,541 as applied to Claims 1, 2, 4-13, 16-20, 22-37 and 41-46 above, and further in view of Szczylik *et al.*

Claims 14 and 38 were canceled in the Amendment filed November 3, 2000 and thus the rejection is moot.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned at (978) 341-0036.

Respectfully submitted,

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MARKED UP VERSION OF AMENDMENTS

Claim Amendments Under 37 C.F.R. § 1.121(c)(1)(ii)

1. (Four Times Amended) A complex comprising semi-purified or pure SV40 VP1 capsid protein or a mixture of VP1 and at least one other SV40 capsid protein; and a non-viral constituent selected from the group consisting of:

a) a purified [an] exogenous [substantially histone-free] DNA, or a purified [an] exogenous [substantially histone-free] DNA encoding an exogenous protein or peptide[product], or a purified [an] exogenous [substantially histone-free] DNA encoding RNA;

b) a vector comprising any of the purified exogenous [substantially histone-free] DNAs of a);

c) a purified [an] exogenous RNA, or a purified [an] exogenous RNA encoding an exogenous protein or peptide[product];

d) a vector comprising any of the purified exogenous RNAs of c); or

e) purified exogenous antisense RNA, purified exogenous ribozyme RNA or any purified exogenous RNA or purified exogenous [substantially histone-free] DNA which inhibits or prevents the expression of undesired protein or proteins in said mammalian cell;

and further comprising operatively linked elements sufficient for one or more of the following:

(i) replication of said constituent;

(ii) expression of said constituent; and

(iii) prevention of expression of said undesired protein or proteins;

in said mammalian cell.

6. (Four Times Amended) A complex according to Claim 1 wherein said non-viral constituent is:

(a) purified exogenous circular or linear [substantially histone-free] DNA;

(b) purified exogenous circular or linear [substantially histone-free] DNA encoding a

protein or peptide[product]; or

(c) purified exogenous circular or linear [substantially histone-free] DNA encoding RNA.

7. (Four Times Amended) A complex according to Claim 6 wherein said purified exogenous [substantially histone-free] DNA is DNA which encodes a protein or peptide[product], wherein said protein or peptide[product] is not made or contained in said cell prior to infection with the construct, or is purified exogenous [substantially histone-free] DNA which encodes a protein or peptide[product], wherein said protein or peptide[product] is made or contained in said cell in an amount insufficient for proper cell function prior to infection with the construct, or is purified exogenous [substantially histone-free] DNA which encodes a protein or peptide[product], wherein said protein or peptide[product] is made or contained in said cell in a form inadequate for proper cell function prior to infection with the construct, or encodes a RNA.

8. (Amended) A complex according to Claim 7 wherein said protein or peptide[product] is an enzyme, a receptor, a structural protein, a regulatory protein or a hormone.

9. (Thrice Amended) A complex according to Claim 1 further comprising SV40 *ori* DNA sequence as a replication regulatory element and further comprising a purified exogenous DNA sequence encoding one or more regulatory elements sufficient for the expression of said exogenous RNA or exogenous protein or peptide in said mammalian cell.

10. (Thrice Amended) A complex according to Claim 1 wherein said constituent is purified exogenous RNA, wherein said purified exogenous RNA is RNA which encodes a protein or peptide[product] which is not made or contained in said cell prior to infection with the construct, or is purified exogenous RNA which encodes a protein or peptide[product] which is made or contained in said cell in an amount insufficient for proper cell function prior to infection with the construct, or is purified exogenous RNA which encodes a protein or peptide[product] which is made or contained in said cell in a form, inadequate for proper cell function prior to infection with the construct, said purified exogenous RNA having regulatory elements, including translation signal or signals sufficient for the translation of said protein or